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To flare or not to flare: patients' and rheumatologists' perceptions on the on-flare retreatment strategy of rituximab in rheumatoid arthritis

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Delphine Bertrand, Anke Deprez, Michaël Doumen, Diederik De Cock, Sofia Pazmino, Anja Marchal, Marc Thelissen, Johan Joly, Elias De Meyst, Barbara Neerinckx, René Westhovens and Patrick Verschueren

Abstract

Background: Several retreatment strategies exist for rituximab in rheumatoid arthritis (RA). In some countries, reimbursement criteria require a loss of disease control for rituximab retreatment. Understanding the patients' and rheumatologists' perceptions regarding this retreatment strategy would be informative in identifying the optimal treatment administration schedule.

Objectives: This study aimed to uncover patients' and rheumatologists' perceptions regarding retreatment strategies of rituximab.

Design: Qualitative study – semi-structured interviews

Methods: Patients with RA, treated with rituximab, and rheumatologists were invited to participate in a qualitative study consisting of individual, in-depth, semi-structured interviews. Interviews were analysed according to the Qualitative Analysis Guide of Leuven.

Results: A total of 16 patients and 13 rheumatologists were interviewed. Benefits (e.g. decreased risk of overtreatment, cost savings and long-lasting effectiveness of rituximab) and barriers (e.g. fluctuating disease activity, slow mode of action and increased glucocorticoid use) of on-flare retreatment were identified. To effectively treat on-flare, flares must first be identified timely. Both stakeholder groups acknowledged that patients are capable of recognizing flares. However, the patient's ability to discriminate between inflammatory and other types of pain was perceived as difficult. Furthermore, patients and rheumatologists stressed that patients must timely seek professional help in case of a flare, followed by a swift response from the rheumatologists. Remarkably, retreatment was approached in various ways among rheumatologists, and not always adhering strictly to the on-flare reimbursement criteria.

Conclusion: This study revealed that both stakeholder groups perceived the heterogeneity in recognition of and reaction to a flare as important in influencing the effectiveness of the on-flare retreatment strategy. Moreover, this study identified the benefits and barriers of treating on-flare, which could be informative for daily practice decisions.

Keywords: perception, qualitative research, retreatment, rheumatoid arthritis, rituximab

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Correspondence to:
Delphine Bertrand
Skeletal Biology and Engineering Research Center, KU Leuven Department of Development and Regeneration, Herestraat 49, Leuven 3000, Belgium
delphine.bertrand@kuleuven.be

Anke Deprez
KU Leuven, Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium

KU Leuven, Department of Public Health and Primary Care, Environment and Health, Leuven, Belgium

Michaël Doumen
Elias De Meyst
Barbara Neerinckx
René Westhovens
Patrick Verschueren
KU Leuven, Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium

UZ Leuven, Rheumatology, Leuven, Belgium

Diederik De Cock
KU Leuven, Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium

Biostatistics and Medical Informatics Research Group, Department of Public Health Sciences, Vrije Universiteit Brussel (VUB), Brussels, Belgium

Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that, if left insufficiently treated, causes functional decline, joint damage and decreased quality of life.[1] Therefore, RA should be treated intensively and therapy should

Sofia Pazmino
KU Leuven, Department of Development and Regeneration, Skeletal Biology and Engineering Research Center, Leuven, Belgium

KU Leuven, Department of Chronic Diseases and Metabolism, Clinical and Experimental Endocrinology, Leuven, Belgium

Anja Marchal
Marc Thelissen
ReumaNet vzw, Zaventem, Belgium

Johan Joly
UZ Leuven, Rheumatology, Leuven, Belgium

be adapted according to a predefined target, namely remission or low disease activity (LDA).[2] One of many treatment options for RA is the biological disease-modifying antirheumatic drug (bDMARD), rituximab. Rituximab is a chimeric monoclonal antibody targeting CD20 on B lymphocytes, consequently causing B-cell depletion.[3] The original dosing schedule for RA was adopted from the treatment of non-Hodgkin lymphoma and consisted of two infusions of 1000 mg with a 2-week interval.[3] However, research showed that a lower dose could be as effective as the original dose.[4–6] Aside from defining the optimal rituximab dose, there is also a need to optimize the administration strategy of rituximab in RA, with several options described in the literature.[7] A first strategy is to readminister rituximab on-demand in case of a flare, either based on the investigator's judgement or a predefined increase in disease activity.[8] This so-called on-flare retreatment strategy could be beneficial as bDMARDs are expensive drugs, implying that treating only in case of a clear relapse could lead to substantial cost savings.[9] On the other hand, the requirement of a flare will inevitably lead to an increase in disease activity and might impact patients' quality of life. Therefore, a second treatment strategy has been proposed based on a fixed interval, for example, every 6 months.[10] This was reported to have more favourable results in terms of controlling disease activity compared to on-flare retreatment.[10] However, infusion intervals vary widely between patients in retrospective observational data,[11] so not all patients seem to need 6-monthly retreatment and treating everyone based on the same fixed interval could cause overtreatment, with consequently excessive immune suppression, in addition to increased costs. A third strategy is to determine the interval between the first two rituximab administrations and subsequently use this interval for fixed retreatment. However, it has been suggested that this interval often extends with an increasing number of cycles, implying that this strategy has its specific limitations.[10,12] Finally, another strategy is to retreat using the treat-to-target (T2T) principle, namely retreating when losing remission or LDA.[8,13] The T2T strategy, based on a target of remission according to a composite disease activity score, has been found to result in better-controlled disease activity compared to on-flare retreatment (⩾8 tender or swollen joints and flaring in the physician's opinion).[8,14] Thus, several retreatment schedules exist, each with its own (dis)advantages, but reimbursement criteria might impose the use of a specific one. For instance, in Belgium, disease activity is required to be above the threshold of LDA [Disease Activity Score in 28 joints (DAS28) of at least 3.2] for patients to be eligible for retreatment with rituximab. We labelled this strategy as an on-flare retreatment strategy and this definition of 'on-flare' is used throughout the paper.

To our knowledge, all studies regarding rituximab retreatment strategies were based on quantitative data and none have explored the perceptions of the different stakeholders. Qualitative research could be informative for shared decision-making between patients and rheumatologists when the balance must be made between efficacy, safety, patient-friendly aspects and costs. Therefore, this study aims to uncover patients' and rheumatologists' perceptions regarding retreatment strategies of rituximab.

Methods

Study design and sample

This study used a qualitative research design, in which patients with RA and rheumatologists were individually interviewed. Patients were recruited from the outpatient clinic at the Rheumatology Department of the University Hospitals Leuven, Belgium, and were eligible for inclusion if they had a diagnosis of RA and were currently or previously treated with rituximab. Additionally, they needed to be able to speak and understand Dutch. In Belgium, to be eligible for rituximab treatment, patients must have failed at least two conventional synthetic DMARDs (csDMARDs) and one tumour necrosis factor inhibitor. A subsequent rituximab administration is only reimbursed when achieving a good or moderate European Alliance of Associations for Rheumatology (EULAR) response 16 weeks after the first rituximab administration, combined with a DAS28-score of at least 3.2 minimally 24 weeks after the previous administration. Rheumatologists from across Belgium were invited *via* email to participate if they were actively treating patients with RA or had done so in the past. Participants were recruited based on purposive sampling to ensure diversity.[15] For patients, age, number of received rituximab cycles, ongoing or discontinued rituximab treatment and dose of rituximab (full or reduced dose) were considered. For rheumatologists, the geographical working location and type of practice (university hospital, general

hospital or private practice) were taken into account. A separate protocol and interview guide for patients and rheumatologists (Supplemental Materials 1 and 2) was developed by the research team together with patient experts and approved by the Ethics Committee Research UZ/KU Leuven (patients: S64778, rheumatologists: MP015897). All participants gave written informed consent. There was no previous relationship between interviewers and interviewees. The study followed the Consolidated Criteria for Reporting Qualitative Research (COREQ) 32-item checklist (Supplemental Material 3).[16]

Data collection

Between February 2021 and May 2021, individual in-depth semi-structured interviews were conducted with one interviewer for the patients (DB), one for the rheumatologists (AD) and two observers (AD/DDC for the patients' and DB/DDC for rheumatologists' interviews). The interview guide consisted of introductory questions, followed by more focused open-ended questions regarding the on-flare retreatment strategy. Due to the COVID-19 pandemic, the interviews were performed *via* video or telephone call, depending on the participants' preferences. Additional participants were interviewed until data saturation was achieved, meaning no new information emerged from the last three interviews. The interviews were audiotaped, whereafter they were transcribed verbatim. Patient characteristics were collected *via* the patients' medical files. Disease activity scores and patient-reported outcomes were taken from the last available visit before the interview. Rheumatologists' characteristics were captured *via* a questionnaire distributed by email, containing questions regarding gender, age, years of experience as a rheumatologist, geographical work location, type of practice and proportion of patients with RA treated with rituximab. After every interview, a debriefing was done between the interviewer and observer(s), and notes were made regarding the participant's behaviour, interview setting and general observations.

Analysis

A thematic analysis was performed according to the Qualitative Analysis Guide of Leuven (QUAGOL).[17,18] QUAGOL is based on the principles of grounded theory and makes use of the constant comparative method.[17] After transcribing the interviews verbatim, the researchers familiarized themselves with the data and wrote ideas down in the margin. Thereafter, the transcripts were coded line-by-line using NVivo 12 software (QSR International, Melbourne, Australia), creating initial codes, which were labels, words or small sentences of a transcript's fragment. Afterwards, similar initial codes were grouped into subthemes and themes. These (sub) themes were refined during peer debriefings and subsequently, they were iteratively discussed by an interdisciplinary research team consisting of rheumatologists, patient experts and researchers. *Via* these meetings, agreement was achieved regarding the final themes and subthemes.

Patient involvement in research

As recommended by EULAR, two patient experts (AM and MT) were involved in the study.[19] After an introduction to the rationale and content of the research project, the patient experts revised the protocol and interview guide and provided feedback on the comprehensibility of the informed consent form. Moreover, they explored the transcripts, gave suggestions on the emerging themes and subthemes, and revised the manuscript.

Results

Participants

In all, 16 patients with RA and 13 rheumatologists were interviewed. All approached patients with RA agreed to participate in the interview. Of the 32 contacted rheumatologists *via* email, 16 did not reply, and two indicated to had no interest in participating. In all, 14 rheumatologists verbally agreed to participate and were numbered accordingly. However, only 13 rheumatologists signed the informed consent form and were interviewed. The mean duration of the interviews was 17 min. Tables 1 and 2 describe the patients' and rheumatologists' characteristics, respectively. Participants explained how they perceived the on-flare retreatment strategy in daily clinical practice. Five overarching themes were generated: 'flare definition', 'recognition', 'reaction', 'balancing benefits and barriers' and 'suggestions'.

Flare definition

The first theme explored how patients and rheumatologists define a flare and its impact on patients' lives (Figure 1). When patients described a flare, they mentioned arising or aggravating

Table 1. Demographic characteristics of interviewed patients.

Characteristics	Patients (*n* = 16)
Age (years)	64.0 (48.0–73.0)
Gender (female)	56% (9/16)
Disease duration (years)	17.0 (3.0–42.0)
Employed (yes)	25% (4/16)
Relationship status	
Single	4
Partner	11
Unknown	1
Having children (yes)[$]	80% (12/15)
Time since last rituximab infusion (months)	7.5 (0.0–44.0)
RF positive	81% (13/16)
ACPA positive	88% (14/16)
Number of rituximab cycles	5.5 (2.0–15.0)
Received at least once a lower dose ($<2 \times 1000$ mg)	25% (4/16)
Discontinued rituximab	13% (2/16)
Concomitant csDMARDs*	63% (10/16)
Concomitant GC*	38% (6/16)
HAQ* (0–3)	1.4 (0.0–3.0)
PGA* (0–100)	31.5 (1.0–66.0)
PhGA* (0–100)	10.0 (0.0–45.0)
DAS28-CRP*	3.4 (1.1–6.2)

Expressed in median (range), % (*n*/*n*) or absolute numbers.
*Data collected on the last available visit before the interview [median (range) time window of 4 (0–35) days between the visit and interview].
[$]For one patient, this information was not available.
ACPA, anti-citrullinated protein antibody; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS28-CRP, disease activity score in 28 joints – C-reactive protein; GC, glucocorticoids; HAQ, health assessment questionnaire; PGA, patient global assessment of disease activity; PhGA, physician global assessment of disease activity; RF, rheumatoid factor.

physical complaints which varied from pain, swelling, stiffness and loss of strength to fatigue. Both patients and rheumatologists mentioned that flares could vary in intensity. Patients believed that not every mild flare needed a retreatment with rituximab. However, in case of intense disease exacerbations, they saw the benefit of treating before the occurrence of a flare:

> It depends on the intensity. If the intensity equals what I have encountered now [intense flare], then I would like it [to be treated before a flare]. However, if this is not the case and only mild (. . .), then I don't think it is necessary [to be treated before the flare]. – Patient 12, female, 60 years

Besides physical complaints, patients underlined the broader impact of a flare. For instance, patients considered a flare to compromise their daily activities, such as opening bottles and cooking. Moreover, they expressed the need for help from their relatives. Several patients added that they experienced a psychological impact during a flare, ranging from frustration and anger to feeling emotional. On the contrary, others did not experience such a mental impact:

> If it [flare] is very intense, then it has a big impact. Yes, you soon get stuck. You cannot do things, you need to ask for help. This feels like a relapse. That gets you down. – Patient 4, female, 54 years

Recognition

The next theme emerging when discussing the process of on-flare retreatment in daily practice was recognizing a flare. Both patients and rheumatologists acknowledged that patients are capable of recognizing a flare themselves and can act upon this. This appeared important to the rheumatologists, as this could diminish the chance of flares getting too intense:

> Some people return [to the consultation] and say 'it is time [for a rituximab infusion]'. The patients can feel it themselves and I don't think that is a bad thing, in the sense that the flare doesn't get too intense. – Rheumatologist 6, male, >60 years

However, perceived difficulties according to rheumatologists and patients were the patient's ability to distinguish between inflammatory and other types of pain not related to a rise in RA disease activity:

> I think that not all patients can estimate correctly if their pain is inflammatory or not. – Rheumatologist 14, female, 41–50 years

On the other hand, patients sometimes felt misunderstood if they sensed a flare which was not reflected in the disease activity scores measured by the rheumatologists. Furthermore, patients indicated that they perceived difficulties recognizing

when a flare was sufficiently intense to require action:

> I think it is difficult to say when it doesn't work anymore, when a flare is present. – Patient 2, male, 63 years

Patients and rheumatologists reported that flares could differ in type of onset, which might impact the choice of the retreatment strategy. In case of a gradual onset, there is ample time to interfere and plan a subsequent rituximab treatment. On the contrary, if the flare has an acute onset, a quick reaction is required, and this might not always be feasible in daily clinical practice. In addition, depending on the intensity, patients sometimes prefer to cope with a flare themselves instead of receiving a subsequent rituximab infusion. The option of self-management, for instance by resting and increasing symptomatic medication, appeared important to patients, at least in case of minor flares:

> Sometimes you have a mild flare. (. . .) In that case, you take a painkiller and the day after the flare is gone, and rest a lot and then it [flare] will be over. – Patient 12, female, 60 years

Reaction

A third theme was the reaction of patients and rheumatologists to the patient's recognition of a flare.

Patient's reaction. Both stakeholders indicated that patients contacted their treating rheumatologists in case of a flare, allowing for an earlier consultation to be scheduled. Nevertheless, patients and rheumatologists underlined the importance of not waiting too long before seeking professional help. For instance, several patients stated that they made this mistake, followed by an intense flare:

> The later [the retreatment], the better. I do not take contact immediately to ask for rituximab as soon as I sense something. I try to postpone it for as long as possible. Of course, waiting too long is also not good, because then the inflammation becomes too strong and it will be difficult to bring it back to a controlled state. – Patient 7, male, 57 years

Rheumatologist's reaction. Both patients and rheumatologists agreed that a swift response by the rheumatologist is required to enable an on-flare retreatment strategy. This strategy would be unacceptable if too much time elapsed between

Table 2. Rheumatologists' characteristics.

Characteristics	Rheumatologists ($n = 13$)
Gender (female)	38% (5/13)
Age (years)	
31–40	31% (4/13)
41–50	46% (6/13)
51–60	15% (2/13)
>60	8% (1/13)
Active as rheumatologists	100% (13/13)
Years active as a rheumatologist	
0–10	46% (6/13)
11–20	38% (5/13)
21–30	8% (1/13)
>30	8% (1/13)
Healthcare practice*	
University hospital	6
General hospital	7
Private practice	3
Estimated number of patients with RA on rituximab	
Unknown	1
0	1
<10	7
10–19	1
⩾20	3
Estimated proportion of patients with RA on rituximab	
0%	1
<3%	5
3–5%	5
6–10%	2

*More than one option is possible.
RA, rheumatoid arthritis.

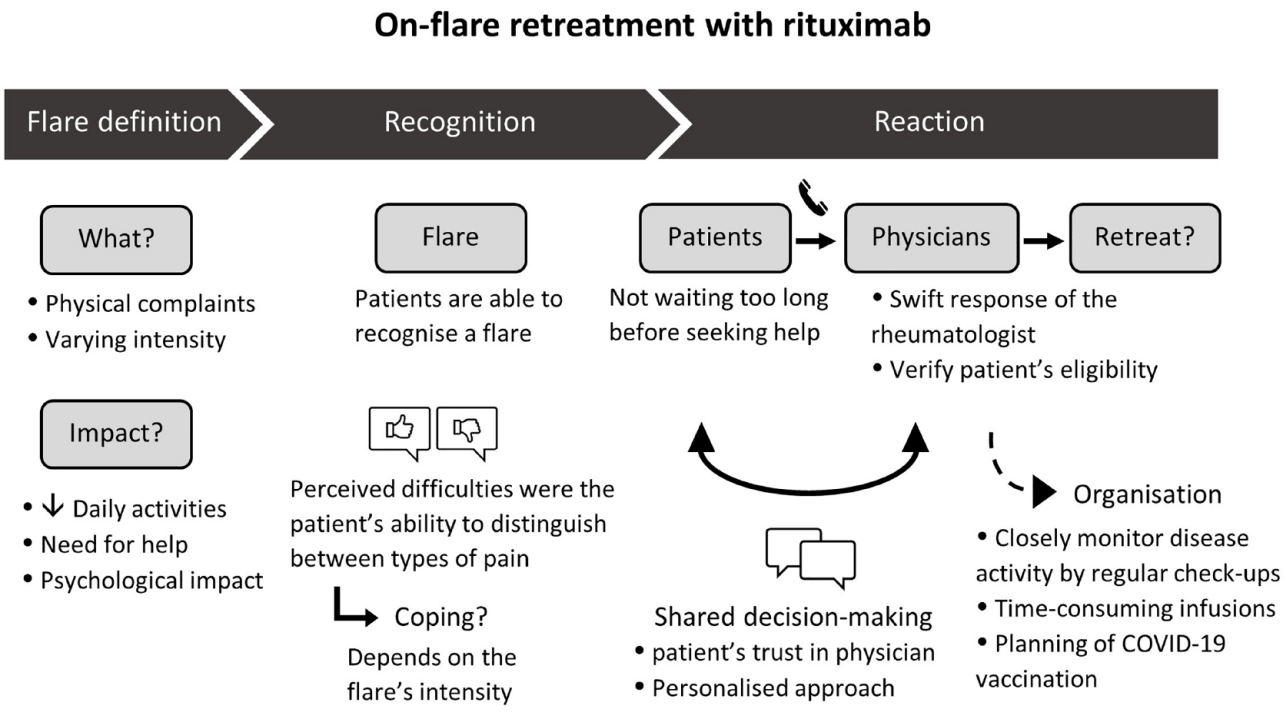

Figure 1. Patients' and rheumatologists' perceptions regarding the on-flare retreatment strategy with rituximab in daily clinical practice.

the notification of a flare and the scheduling of an additional consultation. The next step is to verify the patient's eligibility for the reimbursement criteria. Several rheumatologists agreed with the content of the Belgian reimbursement criteria and stated that a DAS28 score of 3.2 is easily achievable in cases where retreatment is deemed appropriate. In addition, these criteria were perceived as necessary, especially as guidance for inexperienced rheumatologists. Nevertheless, some rheumatologists asked for more flexible criteria, and some acknowledged that they did not know the reimbursement criteria exactly by heart. By contrast, some rheumatologists admitted that in certain circumstances they overruled the disease activity score to comply with the reimbursement criteria, for example, by adding a tender or swollen joint or increasing the patient's global assessment of disease activity. Similarly, one patient realized that the answers to the patient-reported outcomes could heavily influence the eligibility for a subsequent rituximab treatment:

> I find it very difficult to complete this questionnaire [visual analogue scale] and put a line, for pain and fatigue. I feel that if I do not indicate the line sufficiently left or right, then I am no longer eligible [for retreatment]. To what extent can I be objective? – Patient 2, male, 63 years

It appeared that all rheumatologists handled rituximab retreatment in a pragmatic way, from adherence to non-adherence to the on-flare retreatment strategy. Some patients and rheumatologists perceived the on-flare retreatment as a good strategy and did not feel a need for more frequent rituximab administrations. Moreover, it was mentioned that every patient has an optimal retreatment interval, implying that treating everyone with a fixed interval might result in overtreatment in a substantial number of patients. However, one patient and rheumatologist explained that they agreed with the on-flare strategy out of habit:

> I have a couple of patients that have 9 months, one year or the farthest two years [between two rituximab administrations]. Then I think to myself: why for God's sake would I give them rituximab every 6 months? – Rheumatologist 3, female, 31–40 years

On the contrary, some patients and rheumatologists were reluctant towards the on-flare retreatment strategy and would be more inclined to treat

before a flare occurred, as this would decrease disease activity fluctuations and diminish the risk of bone erosions. In addition to fixed retreatment, some alternative retreatment strategies were mentioned by the rheumatologists. For instance, prolonging the interval between rituximab administrations by adding 1 month with every new rituximab cycle. Another suggestion was based on a personalized approach, as rheumatologists perceived that the interval between rituximab administrations became more or less stable in individuals after several infusions. Therefore, they suggested treating patients just before the end of their personal interval and consequently before an imminent flare:

> I would still wait for a flare, but I would let it depend on the patient themselves. If you know that patients, already treated with rituximab for 10 years, present every time with a flare after 9 months, then I would not wait for 9 months, but would retreat that person after 8 months. – Rheumatologist 10, male, 31–40 years

Lastly, a combination of fixed and on-flare retreatment was suggested. Rheumatologists perceived that it could be beneficial to 'hit hard' during the first year and administer rituximab according to a fixed interval every 6 months, followed by an on-flare retreatment for additional rituximab administrations.

Shared decision-making. Patients and rheumatologists underlined that the choice to administer rituximab must be based on shared decision-making. Firstly, patients stated that a consultation is necessary to confirm the patient's perceived flare before readministering rituximab. Moreover, the interviews unfolded the patients' trust in their treating rheumatologists and medical staff. Hence, if rheumatologists decided that rituximab retreatment was necessary, although patients did not subjectively experience the flare, some patients would still agree with their physician. Lastly, rheumatologists explained that they also took the patients' profile, for example, age, multimorbidity and extra-articular manifestations, into account when deciding to prescribe a new rituximab treatment.

Organization. It became clear that the organization of care should be considered when applying an on-flare retreatment strategy. Both patients and rheumatologists underlined that this strategy should be combined with regular consultations to closely monitor the disease activity and identify impending flares. Moreover, the organization of the intravenous rituximab administration was mentioned by both patients and rheumatologists as a barrier owing to the time-consuming infusions. Consequently, several patients were not in favour of fixed retreatment as this would increase the number of hospital visits and time investment. On the other hand, the long infusion times make it more difficult to arrange a rituximab administration on short notice, as time slots need to be available. Therefore, some rheumatologists favoured a fixed retreatment strategy. Lastly, patients and rheumatologists were faced with an unpleasant choice when combining an on-flare retreatment strategy with the planning of the COVID-19 vaccine. They could either wait for the COVID-19 vaccine invitation and postpone the rituximab administration accordingly, risking an intense flare, or administer rituximab in case of a flare and wait several months before COVID-19 vaccination:

> I have to wait for six months before I [receive the COVID-19 vaccine]. I was given the option to either wait for the vaccine or wait for a new rituximab infusion. That was a difficult decision, but then again it wasn't, because I was in need of a rituximab infusion. However, now I have to wait for six months, since it has the opposite action on the immune system, [takes a deep breath] so now I will receive my vaccine around August. – Patient 2, male, 63 years

Balancing benefits and barriers

Benefits. The benefits of an on-flare retreatment strategy were brought forward by patients and rheumatologists (Figure 2). Firstly, participants stressed that rituximab is an effective drug with a long-lasting effect, allowing patients to be less preoccupied with their anti-rheumatic treatment for long periods of time. Furthermore, both stakeholder groups realized that an on-flare retreatment strategy could lower the risk of excessive immune suppression and consequently, lower the infection and safety risk. Additionally, rheumatologists acknowledged that rituximab treatment was associated with a more severe COVID-19 infection risk and therefore emphasized to use of rituximab with caution. Moreover, cost-savings for society motivated patients and rheumatologists to use the on-flare retreatment strategy. Lastly, both stakeholders acknowledged and wanted to respect available scientific evidence.

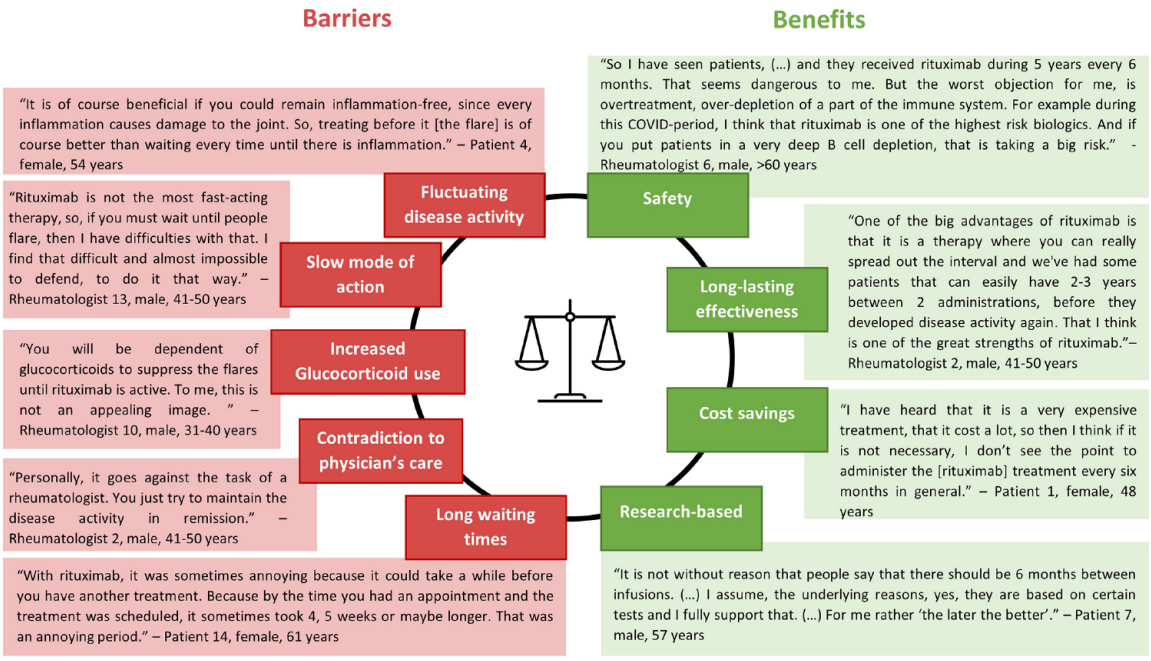

Figure 2. Balancing the perceived benefits and barriers of the on-flare retreatment with rituximab according to patients with RA and rheumatologists.
RA, rheumatoid arthritis.

Barriers. Next to benefits, barriers to the on-flare retreatment strategy were discussed (Figure 2). Firstly, both stakeholder groups stressed that an on-flare retreatment will inevitably lead to undesirable fluctuations in disease activity. Specifically, patients wondered why they should first relapse before receiving a reinfusion, as opposed to being treated while still having a controlled disease activity. With regard to these fluctuations, patients and rheumatologists are worried about the long-term effects of repeated inflammation, for example regarding joint damage. Another reported barrier was the slow-acting mechanism of rituximab, as it takes several weeks before the full benefit of the administration is achieved and, during this time, patients experience ongoing symptoms, unless other measures are taken. Subsequently, concerns were raised by both stakeholder groups about the increased glucocorticoid use to bridge the period between detection of the flare and full activity of rituximab. Moreover, rheumatologists aim to keep patients in remission and prevent RA flares, making them reluctant to adopt this counterintuitive retreatment strategy. Lastly, the on-flare retreatment strategy appeared to be accompanied by several waiting periods from the patient's point of view, namely waiting for a flare, consultation, administration and rituximab's effect.

Balance. All benefits and barriers considered; both patients and rheumatologists emphasized the importance of finding the right balance between advantages and disadvantages to determine the optimal retreatment strategy for rituximab on a patient's case-by-case level. On the other hand, rheumatologists perceived a lack of scientific data regarding different rituximab retreatment strategies, and how to balance their benefits and barriers. Furthermore, they preferred to see evidence of long-term safety to feel comfortable with treating patients based on a fixed interval:

> Firstly, it is an administration of something external to the body. Secondly, a frequency of at least 6 months is mentioned, then 8 months and 12 months will be even better. (. . .) Disadvantage. Other side of the coin is of course you will have some inflammation. Pain that could have been prevented. However, it is a balance, one side compared to the other. You have to find an optimal balance, when the pain is liveable or when an intervention is needed and rituximab should be administered. – Patient 7, male, 57 years

> I am waiting for evidence. I have no clue what the best strategy would be. If I should gamble, I think

> for means of disease control, the fixed retreatment [would be the best]. However, there are lots of other things [that have to be taken into account], there is safety. According to me, that is important. – Rheumatologist 14, female, 41–50 years

Suggestions

Rheumatologists believed that research regarding predictors of flares could enhance the feasibility of the on-flare retreatment strategy. However, they questioned the use of the CD19-count for this purpose. Another suggestion was related to the intravenous administration of rituximab, as this appeared to be an obstacle for some rheumatologists to prescribe rituximab. Therefore, rheumatologists were looking forward to seeing research initiatives regarding subcutaneous administration of rituximab since this is available for other diseases. Finally, both stakeholder groups suggested combining more frequent rituximab administrations with the use of a lower dose, as this might also result in the maintenance of a controlled disease activity:

> I think that a more stable treatment would be beneficial, but maybe combine it with lower dosages instead of administering always the two times one gram. – Rheumatologist 9, male, 31–40 years

Discussion

To our knowledge, this was the first study exploring both patients' and rheumatologists' perceptions regarding an on-flare retreatment strategy for rituximab in RA. From the individual interviews, it seemed that preferences regarding the retreatment strategy varied widely, from being in favour to reluctant towards on-flare retreatment. Participants mentioned both the benefits and barriers of this strategy, which could be informative for decision-making in clinical practice and expressed that these should be weighed against each other on a case-by-case level to determine the optimal retreatment strategy. For instance, rituximab is a long-acting drug, resulting in different retreatment intervals among patients in retrospective cohorts.[11] This induced questions regarding the duration of the optimal retreatment interval and concerns about overtreatment when handling a fixed 6-monthly interval. Especially in the COVID-19 era, it became clear that rituximab needed to be used with caution since it was associated with more severe COVID-19 infections.[20,21] Furthermore, the combination of the unpredictability of a flare and challenges for planning of the COVID-19 vaccines worried rheumatologists since they were recommended to delay vaccinations until at least 6 months after the administration of rituximab.[22,23] Hence, rheumatologists preferred to keep the frequency of rituximab administrations as minimal as possible. Furthermore, a suggestion was made by the patients and rheumatologists to combine fixed retreatment with a lower dose of rituximab, which might reduce the cumulative rituximab dose. Recently, evidence showed that an ultra-low dose of rituximab might be effective for RA treatment and as a result could diminish the risk of overtreatment when combined with a fixed retreatment interval.[5] On the other hand, rheumatologists indicated that they would be more at ease with fixed retreatment when evidence regarding long-term safety becomes available.

Our study suggests that the effectiveness of the on-flare retreatment strategy depends on the reaction to flares of patients as well as rheumatologists. On the one hand, patients must be able to recognize a flare and quickly intervene upon it. However, in reality, it seems that patients often try to postpone a rituximab reinfusion and sometimes wait too long, risking intense flares. This delay in seeking professional help was confirmed by another study.[24] On the other hand, a swift response of the rheumatologist avoiding delay in care was perceived as crucial for the effectiveness of the on-flare retreatment strategy. Consequently, educational initiatives for both stakeholder groups could play an important role in more effective implementation of the on-flare retreatment strategy in daily clinical practice.

What patients and rheumatologists exactly label as a flare remains unclear and could vary between healthcare professionals and patients, which was evident in both this study and previous research.[25] This might have influenced the perceptions of the on-flare retreatment strategy and therefore, it is important to come to a consensus about the flare definition. Furthermore, throughout this paper, we called the retreatment strategy based on the Belgian reimbursement criteria an on-flare strategy as the disease activity was required to increase above a level of LDA, which is a common definition of a flare. However, this might also be considered a T2T strategy since it is based on regular measurement of composite disease activity scores and action is taken as soon as a state of LDA is lost. Despite

this, some rheumatologists and patients seemed to interpret the occurrence of a flare and the need for retreatment somewhat more subjectively, overruling the result of disease activity scores. Thus, it could be beneficial to agree on a uniform, straightforward flare definition that could be applied in both research and daily clinical practice.

The flare's intensity could vary among and within patients and it appeared that a different approach is chosen by the patients depending on the intensity. For instance, if a flare was labelled as mild, patients did not feel the need for rituximab retreatment and preferred to self-manage the flare. This self-management of flares was also described in other studies.[25,26] However, in case of intense flares, the attitude shifted from a preference for self-management to the urgent need for medical evaluation and rituximab retreatment, preferably before the occurrence of a flare. Furthermore, some patients encountered a physical and psychological impact due to the flare, such as impaired daily activities, need for help from relatives and being emotionally unstable, in line with previous research.[24,25]

During the interviews, it was stressed that the decision to retreat with rituximab should be made as a shared decision between patients and rheumatologists. Rheumatologists mentioned taking individual patient factors into account before making retreatment decisions. These findings were in line with the overarching principles of the EULAR recommendations for the management of RA.[2] Moreover, it seemed that rheumatologists handled the retreatment with rituximab in several ways and tried to make it as pragmatic as possible. As a result, rheumatologists had different approaches, and not everyone adhered strictly to the on-flare retreatment strategy as dictated by the Belgian reimbursement criteria. Furthermore, patients and rheumatologists appeared to differentiate fixed 6-monthly retreatment from treating more frequently than with an on-flare approach, in an attempt to prevent flares. One of the suggestions was to retreat based on a personalized interval. However, previous research has indicated that the use of the interval between the first two administrations of rituximab might not be ideal, as intervals might become longer with an increasing number of rituximab administrations.[10,12]

A need for additional research was discussed during the interviews, especially on how to balance the benefits and barriers of rituximab retreatment strategies, and subsequently optimize the rituximab retreatment. Moreover, rheumatologists questioned the lack of approval of a subcutaneous formulation of rituximab for RA despite its availability for other medical conditions. A subcutaneous administration could make the use of rituximab more convenient, as recently exemplified by the bDMARD infliximab.[27,28] This would potentially reduce hospital visits, leading to substantial time-savings, and would consequently lower the patient's burden in addition to reducing healthcare expenditure.[29]

Our study had some limitations. Firstly, all patients were recruited from one university hospital, which might have influenced the results. However, we estimate the impact as rather small because patients were invited to participate based on purposive sampling to ensure diversity. This heterogeneity in patient characteristics is shown in Table 1. Secondly, only individual interviews were performed. Nevertheless, whereas focus groups might have promoted a lively interaction, allowing for more varied perceptions, some participants might feel uncomfortable speaking in groups and are more at ease during individual interviews. Moreover, additional participants were interviewed until data saturation was achieved. Lastly, Belgian reimbursement criteria imply the use of an on-flare retreatment strategy, and therefore, none of the participating patients should have had experience with fixed interval retreatment, which might have influenced their perceptions and negatively impacted the generalizability of our results. However, our study also has several strengths since both stakeholder groups, patients and rheumatologists, were interviewed. Furthermore, results were obtained *via* an inductive, data-driven analysis, implying that themes emerged from the interviews themselves rather than attempting to fit the data into a predefined framework.[18] Lastly, data were analysed according to a qualitative analysis guide, QUAGOL[17] by an interdisciplinary research team, including two patient experts.[30]

The results of our study may stimulate research initiatives investigating the efficacy and safety of different retreatment approaches aiming to determine the optimal retreatment strategy for rituximab, an effective drug for RA treatment.

Conclusion

In summary, this study provides a better understanding of patients' and rheumatologists'

perceptions towards the on-flare retreatment strategy for rituximab. From the interviews, it seemed that patients themselves play a pivotal role in the recognition of flares, and their reaction, in shared decision-making with the rheumatologist, contributes to the effectiveness of the rituximab on-flare retreatment strategy. On the other hand, rheumatologists handle the on-flare retreatment strategy as pragmatically as possible, resulting in varying approaches. Moreover, benefits and barriers of on-flare retreatment were perceived that should be weighed against each other to determine the optimal retreatment strategy on a case-by-case basis, pending the results of further research comparing different retreatment strategies with regards to these risks and benefits. With this study, we hope to raise awareness regarding the need for additional research to optimize the retreatment of rituximab in daily clinical practice.

Declarations

Ethics approval and consent to participate

The study was approved by the Ethics Committee Research UZ/KU Leuven (Patients: S64778, Rheumatologists: MP015897), and all study participants gave their written informed consent before inclusion in the qualitative study.

Consent for publication

Not applicable.

Author contributions

Delphine Bertrand: Conceptualization; Formal analysis; Funding acquisition; Investigation; Methodology; Visualization; Writing – original draft; Writing – review & editing.

Anke Deprez: Conceptualization; Formal analysis; Writing – review & editing.

Michaël Doumen: Formal analysis; Writing – review & editing.

Diederik De Cock: Conceptualization; Formal analysis; Writing – review & editing.

Sofia Pazmino: Formal analysis; Writing – review & editing.

Anja Marchal: Conceptualization; Formal analysis; Writing – review & editing.

Marc Thelissen: Conceptualization; Formal analysis; Writing – review & editing.

Johan Joly: Formal analysis; Writing – review & editing.

Elias De Meyst: Formal analysis; Writing – review & editing.

Barbara Neerinckx: Conceptualization; Formal analysis; Writing – review & editing

René Westhovens: Conceptualization; Formal analysis; Writing – review & editing.

Patrick Verschueren: Conceptualization; Formal analysis; Funding acquisition; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Data are available upon reasonable request.

ORCID iD

Delphine Bertrand https://orcid.org/0000-0003-4330-1447

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